Uptake of cystic fibrosis testing in primary care: supply push or demand pull?

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Abstract

***Objective*—To determine the acceptability and feasibility of screening for carriers of cystic fibrosis in a primary care setting.**

***Design*—Follow up study over 15 months of patients offered carrier testing by mouthwash.**

***Setting*—A general practice in inner London.**

***Subjects*—5529 patients aged 18-45 invited by various methods and combinations of methods (letter, booklet, personal approach) for testing.**

***Main outcome measures*—Uptake of screening, anxiety, and knowledge of test.**

***Results*—957 (17%) invitees were screened over the 15 months. 28 carriers and no carrier couples were detected. Uptake rates were 12% (59/502 patients) among patients invited by letter and tested by appointment; 9% (47/496) among patients invited by letter, with leaflet, and tested by appointment; 4% (128/2953) among patients invited by letter six weeks before the end of the study and tested by appointment; 17% (81/471) among patients offered passive opportunistic testing; 70% (453/649) among patients offered active opportunistic testing; and 25% (22/88) among patients offered active opportunistic testing by appointment. A short term rise in anxiety among those given a positive test result had dissipated by three months. At three months about one fifth and one third of those given positive and negative results respectively did not understand their results correctly.**

***Conclusion*—These results suggest that the strongest variable in determining uptake of screening is the active approach by a health professional offering immediate testing. It remains to be resolved whether the high uptake rates achieved by active recruitment indicate a supply push for this new test rather than a demand from the population.**

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Introduction

The gene responsible for cystic fibrosis was cloned in 1989.[1-3] Although over 200 different mutations within the gene have been described,[4] some 80-85% of all chromosomes bearing cystic fibrosis mutations in the United Kingdom carry one of the four most common mutations.[5,6] Laboratory procedures designed to detect a few common mutations therefore provide a practical method of carrier screening of large populations which is extremely specific but of less than perfect sensitivity.

Genetic carrier screening provides information relevant to subsequent reproduction to allow the widest possible range of informed choice to couples at risk of genetic disorder in their offspring.[7] Such screening, which has no direct effect on the health of the person concerned, is substantially different from other public health screening programmes. Although questionnaire surveys suggest public enthusiasm for cystic fibrosis testing,[8,9] no empirical data were available on whether the public would in general welcome such testing, how well the information gained would be retained, and how it would influence subsequent decisions. It was also unclear whether there would be untoward consequences in the screened population, such as unresolved anxieties or misunderstanding of screening results, leading to inappropriate decisions on subsequent marriage and reproduction. There has also been concern, particularly from the United States, that economic pressures on health care providers may create subtle pressure on couples to be tested or to terminate affected pregnancies.[10]

The most obvious candidates for population based screening programmes for cystic fibrosis carriers are pregnant women attending antenatal clinics and adults of reproductive age registered with a general practice.[11-13] It would seem the most advantageous to screen before conception, and there are two possible approaches—(*a*) to offer the test to all adults of reproductive age and (*b*) to offer the test to adults known to be contemplating pregnancy. This second group may be identified through family planning and pre-conception clinics, but these do not yet cover most of the population. This study therefore aimed at determining the feasibility and acceptability of testing all adults of reproductive age. The study was conducted in a single large general practice in inner London from January 1991 to March 1992 and looked particularly at the efficacy of several different methods of organising a general practice based screening service.

Subjects and methods

Two patient information leaflets were designed—one to accompany the general offer of testing and the other for patients found to be carriers. At several meetings all members of the practice (doctors, nurses, receptionists, and others) were informed of the purpose, background, and operative details of the proposed study. A study coordinator (GD) was appointed, who had been a health visitor in the practice and so was well acquainted with both the staff and the administrative arrangements there. One of us (MM) was a senior partner in the practice.

We identified 5529 patients aged between 18 and 45 from the computerised practice age-sex register. All were offered screening during the study by one of six different methods outlined below. No patient was offered screening by more than one method.

Method 1 was by letter only and testing by appointment. Five hundred and two randomly selected patients were sent a personally addressed letter of invitation, signed by their own general practitioner, inviting them to make an appointment to be tested.

Method 2 was by letter plus leaflet and testing by appointment. Four hundred and ninety six randomly selected patients were sent the same letter as in method 1 plus the leaflet explaining the background to the test in more detail inviting them to make an appointment to be tested.

Methods 1 and 2 were pursued simultaneously. Two weeks after the letters were sent, opportunistic screening was begun.

Method 3 was by passive opportunistic contact and immediate testing. Patients attending the practice for any reason were handed a leaflet by the practice receptionist explaining the test and inviting their

participation. Testing was available immediately.

Method 4 was by active opportunistic contact and immediate testing. Patients in the waiting area were approached by a member of the research team, told about the test personally, and invited to undergo testing at that time.

Method 5 was by active opportunistic contact and testing by appointment. Patients were approached by the same member of the reseach team as in method 4 on attendance in the practice and given an appointment to return for testing.

Method 6—six weeks before the conclusion of the programme all registered patients who had not been approached were sent a letter of invitation. They were asked to telephone within four weeks for an appointment.

A further 370 patients invited by other approaches during the study are not included here.

Questionnaire—Anxiety was measured with a short version of the Spielberger state trait anxiety inventory.[14] This measures general feelings of anxiety, asking, for example, how calm, relaxed, upset, and worried the person feels at the time of completing the questionnaire. Questions were also asked about knowledge of cystic fibrosis and its inheritance.

Mutation screening procedure—Mouthwash samples, collected by agitating 10 ml 4% sucrose in the mouth,[15] were kept refrigerated and transmitted to the laboratory within four days. Cell pellets were lysed in 500 μl 50 mM sodium hydroxide, boiled for 20 minutes, and neutralised with 100 μl 1M TRIS (pH 7·5). DNA was analysed for four of the most common cystic fibrosis mutations, ΔF508, G551D, G542X, and 621+1G→T, by using the multiplex amplification refractory mutation system (ARMS).[16] These four mutations account for 80-85% of all cystic fibrosis mutations in Britain.[5,6] All positive results and over 300 negative results were checked by using separate assays for each mutation, based on band shift analysis,[17] restriction enzyme digestion, or ARMS.[18] In addition, 105 subjects of Jewish ancestry were analysed for the W1282X mutation, which is common in Ashkenazi Jews.[19]

Screening process—All patients accepting screening were asked to complete a baseline questionnaire. They were then counselled by a member of the team, who explained the test and its implications. The session averaged about 10 minutes. The mouthwash sample was collected. Results were provided within about three weeks. All those tested were notified by post, and carriers were additionally sent a leaflet explaining the implications of carrier status and invited to attend for more detailed genetic counselling. Carriers were invited to suggest screening for their partners and close relatives. All those tested received a second questionnaire by post, at the time of receiving their results. A third follow up questionnaire was sent three months later.

Detailed analysis of the questionnaires and a health economic appraisal of the programme are in progress.

Results

A total of 957 of the 5529 (17%) invitees were screened during the 15 months (table). Of 28 carriers (2·9%) who were identified, 26 were of northern European origin. Twenty six of the carriers (93%) were heterozygous for the ΔF508 mutation and two (7%) for the G551D mutation. Twenty five carriers contacted either the research team or their general practitioner after receiving their results. Twenty three accepted a post-counselling appointment, one telephoned to discuss the result, and another consulted her own doctor about the result. Fifteen had partners, of whom 11 were tested. Fourteen first degree relatives were also tested, of whom five were found to be carriers.

Methods of invitation and uptake rate

Method	No* approached	No tested	% Uptake rate (95% confidence interval)
(1) Letter—beginning	502	59	12 (9 to 15)
(2) Letter and booklet	496	47	9 (6 to 12)
(3) Passive opportunistic	471	81	17 (14 to 20)
(4) Active opportunistic—test now	649	453	70 (67 to 73)
(5) Active opportunistic—return visit	88	22	25 (16 to 34)
(6) Letter—end	2953	128	4 (3 to 5)

*370 patients were invited by other approaches, and are not included in this table.

The mean age of those screened was 30·8 years, and of those who declined the offer of testing 32·1 years. Twenty three per cent (637/2772) of women approached for testing accepted compared with 12% (320/2757) of men. A total of 460 (48%) of those tested had a degree or professional training. A personal approach for immediate testing (active opportunistic (method A)) produced by far the highest response rate (70% (453/649 patients)). The same method of recruitment, but with a delayed rather than immediate test appointment (method 5), resulted in a considerable diminution of recruitment (table). All invitations issued by letter achieved very much lower response rates. Including an information leaflet with the letter of invitation made no apparent difference. Return rates for the second and third post-test questionnaires were 74% (704/957) and 70% (674/957), respectively, suggesting good cooperation from those who were tested. In depth analyses, however, were carried out on those who had completed questionnaires at all three time points (n=481: 467 negative test result; 14 positive test result).

There was no difference in anxiety levels before testing between those who subsequently had a positive test result and those who had a negative result. Immediately after receiving their results patients who had tested positive were significantly more anxious than those who had tested negative (repeated measures analysis of variance: $F(2\,958)=3{\cdot}76$; $p<0{\cdot}025$). Three months after receiving these results anxiety levels among the carriers were similar to those of patients who had received a negative result.

Receipt of either a negative or positive result influenced knowledge, carriers retaining more test specific information than patients who received a negative test result (repeated measures analysis of variance: Wilks's approximate F $(2, 474)=3{\cdot}8$; $p<0{\cdot}02$). Three months after testing, however, some of those receiving positive or negative results did not completely understand the meaning of their test result: 17% of those receiving a negative test result (79/467) believed that they were definitely not carriers. Though all those receiving a positive result knew that they had received a positive result, several did not know that this meant that they were definitely carriers. Five of the 14 carriers responding at all study time points believed that a positive result meant that they were only likely to be carriers. All had accepted the offer of post-test counselling.

Discussion

During 15 months of active screening 17% of all adults registered with an inner city general practice had undergone cystic fibrosis screening; 2·9% of these were found to be carriers of the disease. With 80-85% of mutations being detectable in the assay and 85% of the practice population being of northern European descent this is compatible with published estimates of gene frequency in north Europeans (about 4%,

$0{\cdot}04\times0{\cdot}85\times0{\cdot}85=0{\cdot}029$). That no carrier couples were identified in the programme was a matter of chance, given the fairly small numbers, emphasising that screening of total populations must be a long term strategy. There was no evidence of serious lasting anxiety in the heterozygotes who were detected. At three months about one fifth and one third of patients receiving positive and negative results did not understand their results correctly.

Our results are broadly similar to those of Watson *et al.*[12] In another recent study, based on an antenatal clinic, 73% of the eligible population were tested.[10] As this represented an invitation to immediate screening by a midwife during an antental visit it is probably most comparable to the active opportunistic approach in our study (method 4; uptake 70%). The most important variable in screening uptake may therefore be the active approach by a professional offering immediate testing. Whether a pregnant population, more highly motivated to think of issues related to childhood diseases, would respond to less labour intensive recruitment methods such as postal approaches is untested. As very similar uptake rates can be achieved in pregnant and non-pregnant populations, choice between the two must rest on their relative merits. Long term follow up studies are required to determine what those who have been screened in community based programmes recall of their results and the uses they make of this information in subsequent reproductive decisions.

Twice as many women as men agreed to be screened. Possibly many men see carrier testing as associated with reproduction and childbirth and hence more the woman's responsibility. As in the initial phases of most innovations, it was mainly the educated middle classes who came to be tested. The figures from our study are consistent with the view that screening families of known carriers ("cascade" screening) is an efficient method of finding other heterozygotes and should be an integral part of any genetic screening project.[20] During the study 20 members of a family with a history of cystic fibrosis and registered with a neighbouring practice asked to be tested. Six carriers were identified, including one carrier couple.

The differences in uptake between active and passive recruitment have implications for the question of consent and the assessment of public enthusiasm for screening. It is clear from responses to postal invitations that there is not a great public demand for or interest in cystic fibrosis carrier testing. At the end of the study all the doctors and health visitors in the practice were asked how many patients had raised the subject of cystic fibrosis screening with them. Evidently fewer than 100 of the 5529 people offered screening made any reference to the study. This low level of interest was also evident when we offered health professionals carrier testing.[21] Our study does not allow us to assess the degree to which those who respond to a personal approach are motivated by a desire for carrier status information, willingness to accept advice from a health professional provided that it does not entail too much inconvenience, or unwillingness to refuse a polite request from a health professional. The finding that most patients who accept the offer on one day but fail to return on another day for the test supports one or both of the second interpretations.

An important issue, therefore, which remains to be resolved is whether the lack of public willingness to make any more than a minimal effort to seek testing suggests that such testing is not really wanted and that the higher uptake rates achieved by positive recruitment indicate a supply push for this new test rather than a demand from the population.

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